

Birth of the first 100 babies in Hawaii after conception in-vitro: Experience at the Pacific In-Vitro Fertilization Institute

Thomas Huang Jr PhD*†
Philip McNamee MD*†
Thomas Kosasa MD*†
Jana Silva BA†
Ralph W. Hale MD†
Francis Terada MD*†
Benton Chun MD*†
Carl Morton MD*†

This paper reports on the first 100 infants delivered consecutively the result of 63 pregnancies after conception in-vitro at the Pacific In-Vitro Fertilization (IVF) Institute. These pregnancies were established prior to the introduction of embryo-cryopreservation into the program. Ninety-seven percent (97%) of singleton pregnancies delivered after 36 weeks; only 5/31 (16%) required tocolytic therapy. The overall multiple gestation rate was 51%, higher than in many other IVF centers. Maternal complications and neonatal morbidity were associated primarily with these multiple gestations. Forty-one percent (41%) delivered in < 36 weeks, and tocolytics were administered in 22/27 (81%) of twin and 5/5 (100%) of triplet gestations. Neonatal morbidity was noted in 39 infants (33 from multiple gestations); 28 neonates were admitted to the intensive care unit (27 from multiple gestations). Nine births had or developed minor abnormalities (hernias, pyloric stenosis). One case of Trisomy 21, and one infant death at 11 months occurred in the group. The caesarean section rate for all IVF deliveries was 65%. It is concluded that IVF is clearly established in Hawaii for infertility refractory to other methods of treatment. The risk associated with IVF stem from the possibility of multiple gestations, not whether the pregnancy was initiated in-vitro. In the future, embryo cryopreservation may help to reduce the risk of multiple pregnancy.

* Pacific In-Vitro Fertilization Institute, Suite 525

† Department of Obstetrics and Gynecology, University of Hawaii
John A. Burns School of Medicine
Kapiolani Medical Center for Women and Children
1319 Punahou St., Honolulu, Hawaii 96826

Received for publication on October 10, 1990.

Introduction

Human In-Vitro Fertilization is now a well-accepted treatment for infertility due to tubal blockage, endometriosis, male factor, immunologic and idiopathic causes^{1,2}. IVF has been offered in Hawaii since 1985 at the Pacific In-Vitro Fertilization Institute at Kapiolani Medical Center for Women and Children, and most health insurers in the State will provide coverage for at least one complete treatment cycle.

Since the first IVF birth in Hawaii in December 1985, more than 100 babies have been delivered (through July 1990). The overall clinical pregnancy rate at the Institute is high, compared to other programs in the United States¹⁰, but an evaluation of the course of pregnancy and the delivery is also vital in evaluating the efficacy of this rapidly changing technology. This paper retrospectively summarizes data on the course of these first 100 IVF deliveries.

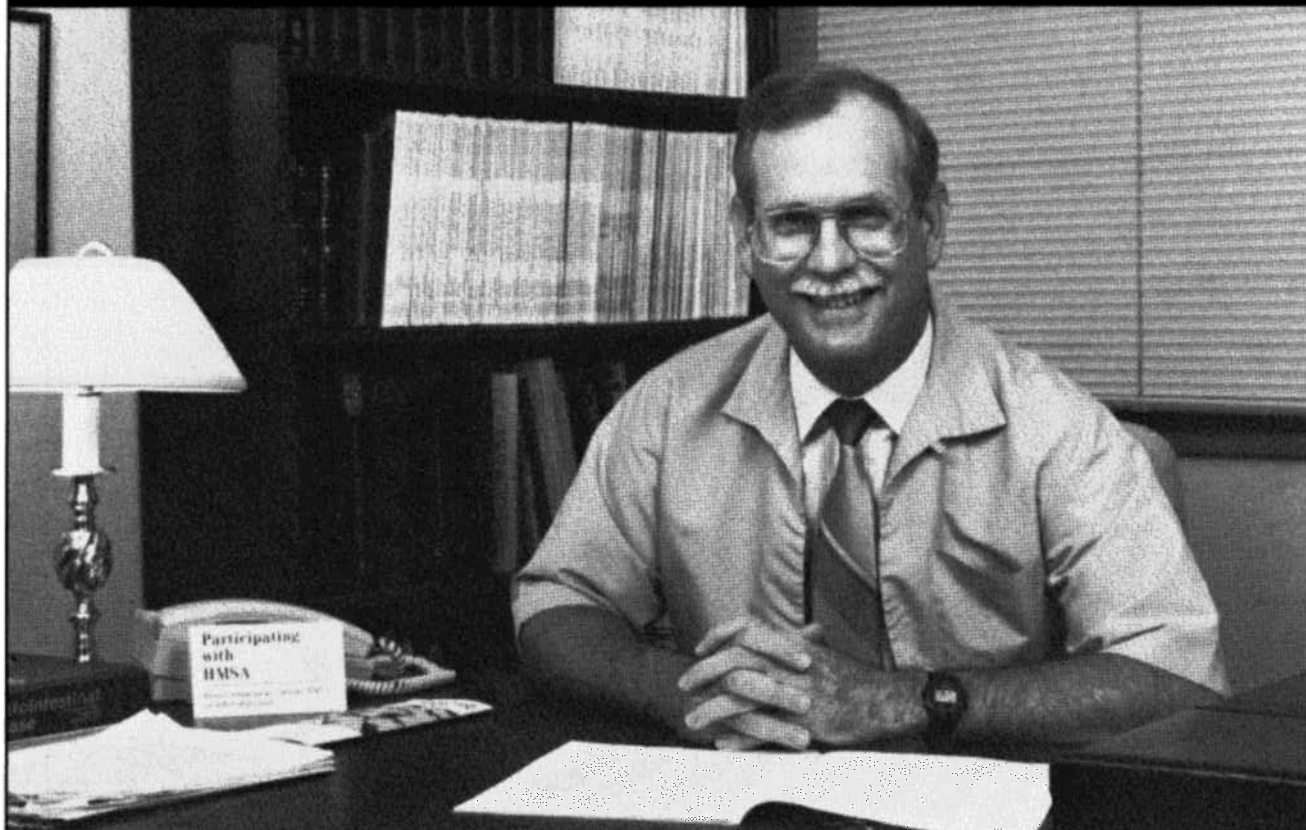
Patients and methods

Data on pregnancy, labor, and delivery and neonatal outcome were obtained from the treatment charts on the first 100 sequential IVF babies born. The average maternal age was 34 years (25-42 yrs). The mean duration of infertility was 6 years. Forty-seven (75%) patients had never delivered a viable fetus prior to IVF and 23 (37%) had never become pregnant.

Induction of ovulation was performed by controlled ovarian hyperstimulation with human menopausal gonadotropin (HMG), beginning either on cycle day 2 or following GnRH agonist (leuprolide acetate) suppression beginning on cycle day 21⁴. Oocytes were harvested either laparoscopically or, since November 1987, routinely while utilizing transvaginal

(Continued) ➤

Why is Dr. William Hartman an HMSA Participating Provider?



**“It’s the right decision for me
and for my patients.”**

HMSA offers health care providers like Dr. Hartman, a gastroenterologist in Honolulu, some very good reasons for joining our Participating Provider Program. Reasons like the competitive advantage he has with access to our more than 600,000 members — 90% of whom choose Participating Providers. Or the payments that he receives directly and promptly from HMSA — that helps his cash flow and eases his administrative expenses.

Like Dr. Hartman, when you participate with HMSA,

you can depend on our staff to provide courteous and professional service. And your patients benefit by knowing in advance what their out-of-pocket costs will be. They feel secure that you and HMSA are working together to keep those costs under control.

If you care about your patients' health care and its cost, being an HMSA Participating

Provider makes sense. For more information on HMSA's Participating Provider Program, call 973-7700 on Oahu or your local HMSA office.



With you all the way.

ultrasonography, as an outpatient procedure. Oocytes were inseminated 4 to 20 hours after retrieval, and transfer of several of the embryos into the uterus was done typically at the 4-cell stage, approximately 48 hours after egg retrieval. Subsequent, early, quantitative HCG tests and real-time ultrasound at 6 weeks confirmed clinical pregnancy. Prenatal care was then carried out by the patient's private obstetrician.

TABLE 1
Infants Delivered

Singleton.....	31
Twin	27
Triplet.....	5
Male	54
Female.....	46

100 infants from 63 deliveries

TABLE 2
Causes of Infertility

Tubal Factor	31 (49%)
Anovulation	7 (11%)
Endometriosis	6 (10%)
Male Factor	4 (6%)
Unexplained	3 (5%)
Multiple Factors (*)	12 (19%)

* including antisperm antibody in several patients

Results

Between December 1985 and July 1990, 100 infants were born in 63 deliveries (Table 1). Multiple gestations accounted for 32/63 (51%) of total pregnancies (27 twins and 5 triplets). The sex ratio was unremarkable (54 males, 46 females). The primary cause of infertility in this cohort had been a tubal factor; other less frequent causes included anovulation, endometriosis, male factor, immunological, and unexplained infertility (Table 2).

Most of the IVF pregnancies (78%) ended with delivery after 36 weeks (Table 3), including 97% of singletons and 59% of the multiple gestations. Of the 14 births occurring prematurely, eg <36 weeks, 13 were multiple. This comprised 41% of all multiple gestations. In the case of twins and triplets, the average gestational ages were 35 and 31.5 weeks respectively. These exhibited a wide range of gestational ages, twins: 21 to 39 wks; triplets: 23 to 36 wks.

Maternal complications included preterm labor, gestational diabetes, active herpes infection, pregnancy-induced hypertension, and premature rupture of the membranes (Table 4). The

TABLE 3
Duration of Gestation

Weeks	Total (n=63)	Singleton (n=31)	Multiple (*) (n=32)
< 28	2 (3%)	0 (0%)	2 (6%)
28-31	5 (8%)	0 (0%)	5 (16%)
32-35	7 (11%)	1 (3%)	6 (19%)
> = 36	49 (78%)	30 (97%)	19 (59%)

* mean gestational ages of 35 and 31.5 weeks for twins and triplets.

TABLE 4
Maternal Complications During Pregnancy

	Total (n=63)	Singleton (n=31)	Twins (n=27)	Triplets (n=5)
Tocolytics required in	32 (51%)	5 (16%)	22 (81%)	5 (100%)
Gestational Diabetes	7 (8%)	2 (6%)	4 (15%)	1 (20%)
Pregnancy-Induced Hypertension	5 (8%)	0 (0%)	4 (15%)	1 (20%)
Premature Rupture of Membranes	4 (6%)	0 (0%)	3 (11%)	1 (20%)
Active Herpes Infection	2 (3%)	2 (6%)	0 (0%)	0 (0%)
First Trimester Vaginal Bleeding	23 (37%)	ND	ND	ND
Postpartum morbidity*	11 (19%)	ND	ND	ND

* includes maternal fever and use of antibiotics; anemia requiring transfusion; transient renal insufficiency.

ND - not determined

latter two occurred only in the multiple pregnancy group. Only 5/31 (16%) of singletons required tocolytic therapy, compared to 22/27 (81%) in twins and 5/5 (100%) in triplets.

Multiple gestation with abnormal presentation was a major reason for the overall caesarean section rate of 65% (Table 5). The caesarean rate for twins and triplets was 89% and 80%, respectively.

Neonatal morbidity was documented in the case of 39 infants that were born (Table 6). Twenty-eight neonates were admitted to the neonatal intensive care unit at Kapiolani Medical Center, almost all the result of multiple births.

The reasons for extended hospitalization included severe prematurity, difficulty in feeding, respiratory problems, the need for antibiotics or hyperbilirubinemia. Two neonatal deaths occurred, one at 23 weeks in a triplet pregnancy and one at 24 weeks in a twin pregnancy. Additionally, 2 cases of intrauterine fetal demise took place, one at 21 weeks in a twin pregnancy, and one at 31 weeks in a triplet pregnancy associated with pregnancy-induced hypertension. Subsequently, one infant died at 11 months of age.

A summary of developmental abnormalities appears in Table 7. Minor abnormalities were observed in 9 (9%) of infants. This included 7 hernias and 2 cases of pyloric stenosis. Seven out of the total occurred in multiple gestations. One case of Trisomy 21 developed in a triplet pregnancy.

Discussion

Since the birth of the first IVF baby in 1978, human in-vitro fertilization has become an ethically and medically accepted treatment for infertility due to tubal disease, endometriosis, male factor, ovulatory dysfunction, immunological infertility and for unexplained causes^{1,2}. Data presented here analyze retrospectively the outcomes in the first 100 IVF babies in Hawaii from the Pacific In-Vitro Fertilization Institute at Kapiolani Medical Center for Women and Children.

The multiple pregnancy rate of 51% reported here is higher than the range of 12 to 35% reported in other programs^{5,9,11}. IVF clinical pregnancy rates upwards of 25%² only are achieved when several embryos are simultaneously transferred. Consequently, this increases the chances for multiple gestations^{5,6,7} which, in turn, are associated with a higher incidence of maternal and fetal complications⁸. The high rate of multiple gestations in our series is probably due to transferring an average of more than 3 embryos at a time. This strategy evolved in response to the one-time-only insurance benefit allowed by most insurers in the State of Hawaii, combined with the lack of embryo-cryopreservation at this stage of the program's development.

At the Pacific IVF Institute, couples are counseled extensively regarding the risks and options, and they participate actively in the choice of the number of embryos at transfer.

Since January 1990, embryo cryopreservation has been offered at the Institute. This may significantly reduce the rate of multiple pregnancies. However, since worldwide experience has shown that a minimum of 3 embryos are required to optimize even singleton pregnancy rates in fresh transfer cycles⁷, the risk of multiple pregnancy will probably continue until non-invasive methods of assessing embryo potential are developed. Until then, systematic identification of other factors pre-

TABLE 5
Indications for Caesarean Sections*

Multiple gestation with abnormal presentation	18
Cephalopelvic disproportion	5
Placenta previa	4
Single pregnancy with abnormal presentation	3
Abruptio placentae	2
Active herpes infection	2
Fetal distress	2
Chorioamnionitis	1
Severe pregnancy-induced hypertension	1
Elective	3

* number of cases. Total n = 41 (65% of cases)

TABLE 6
Neonatal Morbidity and Mortality

Neonatal morbidity*	39 (39%)
Singletons	6 (6%)
Multiples	33 (33%)
Admission to neonatal intensive care unit	28 (29%)
Singletons	1 (1%)
Multiples	27 (27%)
Neonatal mortality	2 (0%)
Infant mortality	1 (1%)

* causes include severe prematurity, difficulty in feeding, respiratory problems, use of antibiotics and severe hyperbilirubinemia.

** at 11 months of age.

TABLE 7
Infant Abnormalities

Minor:	
hernia	7
pyloric stenosis	2
Major:	
Trisomy 21	1

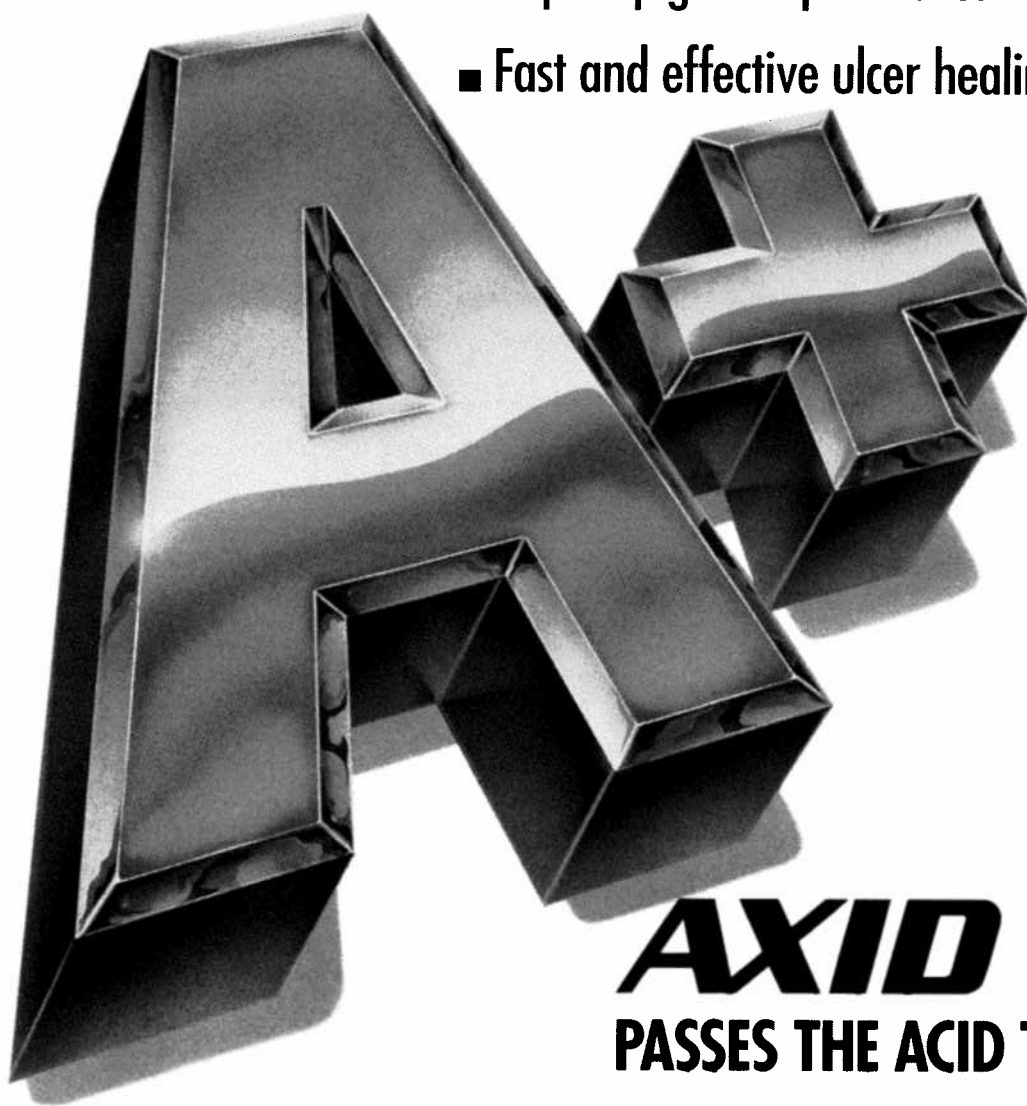
(Continued) ►

For excellent response in the treatment of
duodenal ulcers...

AXID[®] nizatidine

has the right answers

- Rapid epigastric pain relief^{1,2*}
- Fast and effective ulcer healing^{2,3,4}



AXID
PASSES THE ACID TEST

*Most patients experience pain relief with the first dose.
See adjacent page for references and brief summary
of prescribing information.

NZ-2943-B-149347

© 1991, ELI LILLY AND COMPANY

AXID® (nizatidine capsules)

Brief Summary. Consult the package insert for complete prescribing information.

Indications and Usage: 1. Active duodenal ulcer—for up to 8 weeks of treatment. Most patients heal within 4 weeks.

2. Maintenance therapy—for healed duodenal ulcer patients at a reduced dosage of 150 mg h.s. The consequences of therapy with Axid for longer than 1 year are not known.

Contraindications: Known hypersensitivity to the drug. Because cross sensitivity in this class of compounds has been observed, H₂-receptor antagonists, including Axid, should not be administered to patients with a history of hypersensitivity to other H₂-receptor antagonists.

Precautions: General—1. Symptomatic response to nizatidine therapy does not preclude the presence of gastric malignancy.

2. Dosage should be reduced in patients with moderate to severe renal insufficiency.

3. In patients with normal renal function and uncomplicated hepatic dysfunction, the disposition of nizatidine is similar to that in normal subjects.

Laboratory tests—False-positive tests for urobilinogen with Multistix® may occur during therapy.

Drug Interactions—No interactions have been observed with theophylline, chlordiazepoxide, lorazepam, lidocaine, phenytoin, and warfarin. Axid does not inhibit the cytochrome P-450 enzyme system; therefore, drug interactions mediated by inhibition of hepatic metabolism are not expected to occur. In patients given very high doses (3,900 mg) of aspirin daily, increased serum salicylate levels were seen when nizatidine, 150 mg b.i.d., was administered concurrently.

Carcinogenesis, Mutagenesis, Impairment of Fertility—A 2-year oral carcinogenicity study in rats with doses as high as 500 mg/kg/day (about 80 times the recommended daily therapeutic dose) showed no evidence of a carcinogenic effect. There was a dose-related increase in the density of enterochromaffin-like (ECL) cells in the gastric oxyntic mucosa. In a 2-year study in mice, there was no evidence of a carcinogenic effect in male mice, although hyperplastic nodules of the liver were increased in the high-dose males as compared with placebo. Female mice given the high dose of Axid (2,000 mg/kg/day, about 330 times the human dose) showed marginally statistically significant increases in hepatic carcinoma and hepatic nodular hyperplasia with no numerical increase seen in any of the other dose groups. The rate of hepatic carcinoma in the high-dose animals was within the historical control limits seen for the strain of mice used. The female mice were given a dose larger than the maximum tolerated dose, as indicated by excessive (30%) weight decrement as compared with concurrent controls and evidence of mild liver injury (transaminase elevations). The occurrence of a marginal finding at high dose only in animals given an excessive and somewhat hepatotoxic dose, with no evidence of a carcinogenic effect in rats, male mice, and female mice (given up to 360 mg/kg/day, about 60 times the human dose), and a negative mutagenicity battery are not considered evidence of a carcinogenic potential for Axid.

Axid was not mutagenic in a battery of tests performed to evaluate its potential genetic toxicity, including bacterial mutation tests, unscheduled DNA synthesis, sister chromatid exchange, mouse lymphoma assay, chromosome aberration tests, and a micronucleus test.

In a 2-generation, perinatal and postnatal fertility study in rats, doses of nizatidine up to 650 mg/kg/day produced no adverse effects on the reproductive performance of parental animals or their progeny.

Pregnancy—Teratogenic Effects—Pregnancy Category C—Oral reproduction studies in rats at doses up to 300 times the human dose and in Dutch Belted rabbits at doses up to 55 times the human dose revealed no evidence of impaired fertility or teratogenic effect; but, at a dose equivalent to 300 times the human dose, treated rabbits had abortions, decreased number of live fetuses, and depressed fetal weights. On intravenous administration to pregnant New Zealand White rabbits, nizatidine at 20 mg/kg produced cardiac enlargement, coarctation of the aortic arch, and cutaneous edema in 1 fetus, and at 50 mg/kg, it produced ventricular anomaly, distended abdomen, spina bifida, hydrocephaly, and enlarged heart in 1 fetus. There are, however, no adequate and well-controlled studies in pregnant women. It is also not known whether nizatidine can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Nizatidine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers—Studies in lactating women have shown that 0.1% of an oral dose is secreted in human milk in proportion to plasma concentrations. Because of growth depression in pups reared by treated lactating rats, a decision should be made whether to discontinue nursing or the drug, taking into account the importance of the drug to the mother.

Pediatric Use—Safety and effectiveness in children have not been established.

Use in Elderly Patients—Healing rates in elderly patients were similar to those in younger age groups as were the rates of adverse events and laboratory test abnormalities. Age alone may not be an important factor in the disposition of nizatidine. Elderly patients may have reduced renal function.

Adverse Reactions: Clinical trials of varying durations included almost 5,000 patients. Among the more common adverse events in domestic placebo-controlled trials of over 1,900 nizatidine patients and over 1,300 on placebo, sweating (1% vs 0.2%), urticaria (0.5% vs <0.01%), and somnolence (2.4% vs 1.3%) were significantly more common with nizatidine. It was not possible to determine whether a variety of less common events were due to the drug.

Hepatic—Hepatocellular injury (elevated liver enzyme tests or alkaline phosphatase) possibly or probably related to nizatidine occurred in some patients. In some cases, there was marked elevation (>500 IU/L in SGOT or SGPT and, in a single instance, SGPT was >2,000 IU/L). The incidence of elevated liver enzymes overall and elevations of up to 3 times the upper limit of normal, however, did not significantly differ from that in placebo patients. All abnormalities were reversible after discontinuation of Axid. Since market introduction, hepatitis and jaundice have been reported. Rare cases of cholestatic or mixed hepatocellular and cholestatic injury with jaundice have been reported with reversal of the abnormalities after discontinuation of Axid.

Cardiovascular—In clinical pharmacology studies, short episodes of asymptomatic ventricular tachycardia occurred in 2 individuals administered Axid and in 3 untreated subjects.

CNS—Rare cases of reversible mental confusion have been reported.

Endocrine—Clinical pharmacology studies and controlled clinical trials showed no evidence of antiandrogenic activity due to nizatidine. Impotence and decreased libido were reported with equal frequency by patients on nizatidine and those on placebo. Gynecomastia has been reported rarely.

Hematologic—Fatal thrombocytopenia was reported in a patient treated with nizatidine and another H₂-receptor antagonist. This patient had previously experienced thrombocytopenia while taking other drugs. Rare cases of thrombocytopenic purpura have been reported.

Integumentary—Sweating and urticaria were reported significantly more frequently in nizatidine- than in placebo-treated patients. Rash and exfoliative dermatitis were also reported.

Hypersensitivity—As with other H₂-receptor antagonists, rare cases of anaphylaxis following nizatidine administration have been reported. Rare episodes of hypersensitivity reactions (eg, bronchospasm, laryngeal edema, rash, and eosinophilia) have been reported.

Other—Hyperuricemia unassociated with gout or nephrolithiasis was reported. Eosinophilia, fever, and nausea related to nizatidine have been reported.

Overdosage: Overdoses of Axid have been reported rarely. If overdosage occurs, activated charcoal, emesis, or lavage should be considered along with clinical monitoring and supportive therapy. Renal dialysis does not substantially increase clearance of nizatidine due to its large volume of distribution.

PV 2091 AMP
[091190]

References

1. Data on file, Lilly Research Laboratories.
2. *Scand J Gastroenterol* 1987;22(suppl 136):61-70.
3. *Scand J Gastroenterol* 1987;22(suppl 136):47-55.
4. *Am J Gastroenterol* 1989;84:769-774.

NZ-2943-B-149347

Additional information available to the profession on request.



Eli Lilly and Company
Indianapolis, Indiana
46285

IN-VITRO BIRTHS (Continued from page 361)

disposing to multiple IVF pregnancies, eg, maternal age, prior history of pregnancy, etc, may, in conjunction with cryopreservation, help to reduce the risk of multiple pregnancy.

Data indicate that multiple gestations account for the majority of maternal complications. The 22% pre-term delivery rate (<36 weeks) observed here is similar to that reported from other programs^{9,10,12,13}. As expected, the rate was much higher for multiple gestations (41%) than for singletons (3%). However, older maternal age, in addition to multiple gestation, probably contributes to a high pre-term incidence of labor and delivery compared to primiparous patients who are not infertile. The incidence of first trimester bleeding, pregnancy-induced hypertension, premature rupture of membranes, and gestational diabetes is lower in our cohort than has been reported elsewhere¹⁰. Our data support the conclusions by Barlow et al¹⁴ and Hill et al¹³ that such complications are no more prevalent than in other populations of patients with infertility treated by other means. However, the comparatively high use of tocolytics reported in our series (51% of cases) is most certainly due to the relatively higher rate of multiple gestations than has been reported in other centers.

The higher multiple pregnancy rate also accounted for a high overall caesarean section rate (65%); 89% and 80% of twin and triplet pregnancies respectively, were delivered by caesarean section. Other authors have reported overall caesarean section rates of 33 to 56% in IVF gestations^{9,11,12}.

The overall incidence of neonatal morbidity (9%) is nearly identical to that reported by Yeh et al¹⁰ who reported an 8.6% incidence, including pyloric stenosis, bilateral inguinal hernias and tibial torsion. Hernias and pyloric stenosis occurred in our series.

Summary

There have now been more than 100 live births from in-vitro fertilization performed at the Pacific In-Vitro Fertilization Institute at Kapiolani Medical Center for Women and Children in Honolulu. Although our overall clinical pregnancy rates are comparable or better than those at other well-established programs on the Mainland, multiple gestation remains one of the major challenges associated with higher rates of pregnancy. The rates and types of complications, however, are similar to those reported in other IVF centers and for other treatment modalities for infertility. Clearly, it is the presence of multiple gestations, and not whether the pregnancy was initiated in vitro, that should be viewed as the most important risk factor for complications in women with infertility who are treated by IVF¹³. Advances in embryo-cryopreservation and the identification of risk factors may help to reduce the incidence of multiples in the future.

ACKNOWLEDGEMENTS

The authors would like to thank the many institutions and individuals who have directly or indirectly contributed to the work reported here. This includes the directors and staff of Kapiolani Medical Center for Women and Children, the University of Hawaii John Burns School of Medicine, the Hawaii State Legislature and the office of Governor John Waihee. The authors also thank the following members of the office and laboratory staff of the Pacific IVF Institute without whose

(Continued) ►

YOCON®

YOHIMBINE HCl

Description: Yohimbine is a 3a-15a-20B-17a-hydroxy Yohimbine-16a-carboxylic acid methyl ester. The alkaloid is found in Rubiaceae and related trees. Also in Rauwolfia Serpentina (L) Benth. Yohimbine is an indolalkylamine alkaloid with chemical similarity to reserpine. It is a crystalline powder, odorless. Each compressed tablet contains (1/12 gr.) 5.4 mg of Yohimbine Hydrochloride.

Action: Yohimbine blocks presynaptic alpha-2 adrenergic receptors. Its action on peripheral blood vessels resembles that of reserpine, though it is weaker and of short duration. Yohimbine's peripheral autonomic nervous system effect is to increase parasympathetic (cholinergic) and decrease sympathetic (adrenergic) activity. It is to be noted that in male sexual performance, erection is linked to cholinergic activity and to alpha-2 adrenergic blockade which may theoretically result in increased penile inflow, decreased penile outflow or both.

Yohimbine exerts a stimulating action on the mood and may increase anxiety. Such actions have not been adequately studied or related to dosage although they appear to require high doses of the drug. Yohimbine has a mild anti-diuretic action, probably via stimulation of hypothalamic centers and release of posterior pituitary hormone.

Reportedly, Yohimbine exerts no significant influence on cardiac stimulation and other effects mediated by B-adrenergic receptors, its effect on blood pressure, if any, would be to lower it; however no adequate studies are at hand to quantitate this effect in terms of Yohimbine dosage.

Indications: Yocon® is indicated as a sympatholytic and mydriatic. It may have activity as an aphrodisiac.

Contraindications: Renal diseases, and patient's sensitive to the drug. In view of the limited and inadequate information at hand, no precise tabulation can be offered of additional contraindications.

Warning: Generally, this drug is not proposed for use in females and certainly must not be used during pregnancy. Neither is this drug proposed for use in pediatric, geriatric or cardio-renal patients with gastric or duodenal ulcer history. Nor should it be used in conjunction with mood-modifying drugs such as antidepressants, or in psychiatric patients in general.

Adverse Reactions: Yohimbine readily penetrates the (CNS) and produces a complex pattern of responses in lower doses than required to produce peripheral a-adrenergic blockade. These include, anti-diuresis, a general picture of central excitation including elevation of blood pressure and heart rate, increased motor activity, irritability and tremor. Sweating, nausea and vomiting are common after parenteral administration of the drug.^{1,2} Also dizziness, headache, skin flushing reported when used orally.^{1,3}

Dosage and Administration: Experimental dosage reported in treatment of erectile impotence.^{1,3,4} 1 tablet (5.4 mg) 3 times a day, to adult males taken orally. Occasional side effects reported with this dosage are nausea, dizziness or nervousness. In the event of side effects dosage to be reduced to 1/2 tablet 3 times a day, followed by gradual increases to 1 tablet 3 times a day. Reported therapy not more than 10 weeks.³

How Supplied: Oral tablets of Yocon® 1/12 gr. 5.4 mg in bottles of 100's NDC 53159-001-01 and 1000's NDC 53159-001-10.

References:

1. A. Morales et al., New England Journal of Medicine: 1221, November 12, 1981.
2. Goodman, Gilman — The Pharmacological basis of Therapeutics 6th ed., p. 176-188. McMillan December Rev. 1/85.
3. Weekly Urological Clinical letter, 27:2, July 4, 1983.
4. A. Morales et al., The Journal of Urology 128: 45-47, 1982.

Rev. 1/85



AVAILABLE AT PHARMACIES NATIONWIDE

**PALISADES
PHARMACEUTICALS, INC.**

219 County Road
Tenafly, New Jersey 07670
(201) 569-8502
1-800-237-9083

IN-VITRO BIRTHS (Continued from page 363)

vision, dedication, and tireless efforts this program would not exist: Terry Adcock, Pam Judy, Lisa Ontai, Gayle Kogleman, Robin Rose, Kathy Munemasa, Brenda Kaneoka, Anne Henry, Anne Carwyle, Bev Quon, Gayle Suzuki, Kim Okazaki, Jocelyn Won, Lawrene Quisano, Roxanne Ishii and Lisa Bertsch.

REFERENCES

1. Ethical Considerations of the New Reproductive Technologies. *Fertil Steril* 1990, 53 (suppl. 2):37s.
2. Laufer N, Grunfeld L, Garrisi GJ. In-Vitro Fertilization. *Infertility, A Comprehensive Text*, M Seibel (ed) Appleton and Lange, Norwalk Conn., 1990, pp. 481-512.
3. Consumer protective issues involving in vitro fertilization clinics. Hearing before the committee on small business, House of Representatives, March 9, 1989, U.S. Government Printing Office. Serial No. 101-5.
4. Meldrum DR, Wisot A, Hamilton F, Guttay AL, Kempton W, Huynh D. Routine pituitary suppression with leuprolide before ovarian stimulation for oocyte retrieval. *Fertil Steril* 1989, 51:455-459.
5. Kerin JF, Quinn PJ, Kirby C, Seamark RF, Warnes GM, Feffrey R, Matthews CD, Cox LW. Incidence of multiple pregnancy after in-vitro fertilization and embryo transfer. *Lancet* Sept. 3, 1983.
6. Hershtag A, Floch JA, DeCherney AH, Lavy G. Comparison of singleton and multiple pregnancies in In-Vitro Fertilization (IVF) and embryo transfer (ET). *J In-Vitro Fert* 1990, 7:157-159.
7. Edwards RG. In-Vitro Fertilization and Embryo Replacement: Opening Lecture. *Ann NY Acad Sci* 1985, 442: 1-22.
8. Newton M. Other complications of labor. *Textbook of Obstetrics and Gynecology*, DN Danforth (ed), Second edition, 1971, Harper and Row, New York, pp. 662-672.
9. Australian IVF Collaborative Group: High incidence of pre-term births and early losses in pregnancy after in-vitro fertilization. *Br Med J* 1985, 291:1169-1174.
10. Yeh J, Leipzig S, Friedman, EA, Seibel MM. Results of In-Vitro Fertilization pregnancies: Experience at Boston's Beth Israel Hospital. *Int J Fert* 1990, 35:116-119.
11. Frydman R, Belaisch-Allart J, Fries N et al. An obstetric assessment of the first 100 births from the in-vitro fertilization program at Clamart, France. *Am J Obstet Gynecol* 1986, 154:550-555.
12. Andrews MC, Muasher SJ, Levy DL, et al. An analysis of the obstetric outcome of 125 consecutive pregnancies conceived in-vitro and resulting in 100 deliveries. *Amer J Obstet Gynecol* 1986, 154:848-853.
13. Hill GA, Bryan S, Herbert CM, Shaw DM, Wenz AC. Complications of pregnancy in infertile couples: Routine treatment versus assisted reproduction. *Obstet Gynec* 1990, 75:790794.
14. Barlow P, Lejeune B, Puissant F, et al. Early pregnancy loss and obstetrical risk after in-vitro fertilization and embryo transfer. *Hum Rep* 1988, 3:671-675.

MISSION (Continued from page 357)

warmers, to used anesthesia machines and OR tables.

We expect that the interchange of ideas and techniques between the Chinese and the Hawaii volunteers will be mutually beneficial. We have undoubtedly as much to learn from them, as they do from us. The Mission promises to be an exciting opportunity to help others in need.

The Board of Directors of this foundation consists of the following members: C. K. Yeo MD, Pon-sang Chan MD, Ming Chen MD, David Lee, Lester Leu Esq, Edward Ngan, Cheng-Hock Seah MD, George Shimomura MD, Ramon Sy MD, Brad Wong MD, Lockwood Young MD and Lisa A. Wong, Executive Administrator.